

Incidence of Adenocarcinoma of the Esophagus Among White Americans by Sex, Stage, and Age

Linda Morris Brown, Susan S. Devesa, Wong-Ho Chow

Rapid increases in the incidence of adenocarcinoma of the esophagus have been reported among white men. We further explored the temporal patterns of this disease among white individuals by sex, stage, and age by use of data from the Surveillance, Epidemiology, and End Results program. We identified 22759 patients from January 1, 1975, through December 31, 2004, with esophageal cancer, of whom 9526 were diagnosed with adenocarcinoma of the esophagus. Among white men, increases in the incidence of esophageal cancer were largely attributed to a 463% increase in the incidence of adenocarcinoma over this time period, from 1.01 per 100 000 person-years (95% confidence interval [CI] = 0.90 to 1.13) in 1975–1979 to 5.69 per 100 000 person-years (95% CI = 5.47 to 5.91) in 2000–2004. A similar rapid increase was also apparent among white women, among whom the adenocarcinoma rate increased 335%, from 0.17 (95% CI = 0.13 to 0.21) to 0.74 per 100 000 person-years (95% CI = 0.67 to 0.81), over the same time period. Adenocarcinoma rates rose among white men and women in all stage and age groups, indicating that these increases are real and not an artifact of surveillance.

J Natl Cancer Inst 2008;100:1184–1187

Total esophageal cancer incidence and mortality have been increasing among white men, stable among white women, and decreasing in black men and women (1). It is projected that there will be 16470 new patients diagnosed with esophageal cancer and 14280 deaths from it in 2008 (2). Rapid increases in the incidence of adenocarcinoma of the esophagus have been reported in the United States, with rates highest among white males (3–6). These patterns are in contrast to those for squamous cell carcinoma of the esophagus, for which rates have been considerably higher among blacks than whites and have been declining in recent decades. To better understand the temporal patterns and to assess the potential influence of heightened surveillance for adenocarcinoma we performed a detailed examination of the temporal trends among white individuals by sex, stage, and age. Esophageal adenocarcinoma cases among blacks (211) and other races (185) were too few for in-depth analyses.

Data from nine population-based registries in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (1) were used to calculate incidence rates of primary invasive esophageal cancer (*International Classification of Diseases for Oncology*, 3rd edition, topography codes 150–159) for 22759 white

patients diagnosed during the period from January 1, 1975, through December 31, 2004, in six 5-year time periods (ie, 1975–1979 through 2000–2004) (7). The nine registries, accounting for approximately 10% of the US population, are located in the metropolitan areas of Atlanta, Detroit, San Francisco–Oakland, and Seattle–Puget Sound and the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah. All SEER Registries annually meet the Gold Standard Registry Certification from the North American Association of Central Cancer Registries, Inc, for completeness (at least 95%), accuracy (<3% of cases identified through death certificates only), and timeliness of data. Age-adjusted rates (using the 2000 US standard) and 95% confidence intervals (CIs) were calculated by sex and histological type (adenocarcinoma, morphology codes 8140–8575; squamous cell carcinoma, codes 8050–8084) by use of SEER*Stat software (8). Age-adjusted rates by stage (local, regional, distant, and unknown, as indicated by SEER historic stage A) and age-specific rates (age groups 25–44, 45–54, 55–64, 65–74, and ≥75 years) were calculated for adenocarcinoma by sex. All rates were expressed per 100 000 person-years, and only data points with at least 10 observations were presented. Temporal trends

were plotted so that a slope of 10 degrees represented a change of 1% per year (ie, 40 years on the horizontal axis is the same length as one logarithmic cycle on the vertical axis) (9).

During the time period 1975–2004, 22759 white patients were diagnosed with esophageal cancer (16493 men and 6266 women), of whom 9526 were diagnosed with adenocarcinoma (8128 men and 1398 women). Among white men, total age-adjusted esophageal cancer rates increased steadily from 5.76 per 100 000 person-years (95% CI = 5.49 to 6.03) during 1975–1979 to 8.34 per 100 000 person-years (95% CI = 8.08 to 8.60) during 2000–2004, largely because of a 463% increase in adenocarcinoma rates from 1.01 (95% CI = 0.90 to 1.13) to 5.69 (95% CI = 5.47 to 5.91) (Table 1 and Figure 1). The incidence of squamous cell carcinoma decreased 50% across the study period, from 3.81 per 100 000 person-years (95% CI = 3.59 to 4.03) in 1975–1979 to 1.90 per 100 000 person-years (95% CI = 1.77 to 2.03) in 2000–2004. With the decreases in squamous cell carcinoma and the increases in adenocarcinoma, the rate for adenocarcinoma among white men surpassed that for squamous cell carcinoma around 1990. Among white women, total esophageal cancer rates remained constant at around 2.0 per 100 000 person-years during the time period 1975–2004, attributable to a 29% decrease in squamous cell carcinoma from 1.38 per 100 000 person-years (95% CI = 1.28 to 1.50) during 1975–1979 to 0.98 per 100 000 person-years in 2000–2004 (95% CI = 0.90 to 1.06) and a 335% increase in adenocarcinoma from 0.17 per 100 000 person-years (95% CI = 0.13 to 0.21) in 1975–1979 to 0.74 per 100 000 person-years in 2000–2004 (95% CI = 0.67 to 0.81). The gap between squamous cell

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD (LMB, SSD, W-HC); RTI International, Rockville, MD (LMB).

Correspondence to: Linda Morris Brown, MPH, DrPH, RTI International, 6110 Executive Blvd, Suite 902, Rockville, MD 20852-3907 (email: lindabrown@rti.org).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djn211

Published by Oxford University Press 2008.

CONTEXT AND CAVEATS

Prior knowledge

Rapid increases in the incidence of adenocarcinoma of the esophagus have been reported among white men.

Study design

Registry study in which data from the Surveillance, Epidemiology, and End Results program from January 1, 1975, through December 31, 2004, was used to explore the temporal patterns of this disease among white individuals by sex, stage, and age.

Contribution

Adenocarcinoma incidence rates rose from 1975 through 2004 among white men and women in all stage and age groups. The incidence of adenocarcinoma among white men increased 463%, from 1.01 per 100 000 person-years in 1975–1979 to 5.69 per 100 000 person-years in 2000–2004. A similar rapid increase was also apparent among white women, with an increased incidence of 335% from 0.17 per 100 000 person-years to 0.74 per 100 000 person-years.

Implications

Because the increases in incidence are independent of stage and age group, they appear to be real and not an artifact of surveillance.

Limitations

Cases of adenocarcinoma may have been missed or misclassified. Data for the most recent years may have been underreported. Pathological diagnoses were not reviewed centrally.

From the Editors

carcinoma and adenocarcinoma continued to narrow because rates in 2004 were 1.13 per 100 000 person-years (95% CI = 0.95 to 1.34) and 0.84 per 100 000 person-years (95% CI = 0.68 to 1.02), respectively.

Stage-specific adenocarcinoma rates among men increased steadily over the entire time period, and the slopes were remarkably similar, regardless of whether the men were diagnosed with localized (from 0.20 per 100 000 person-years in 1975–1979 to 1.48 per 100 000 person-years in 2000–2004), regional (from 0.28 to 1.86 per 100 000 person-years), or distant-stage (from 0.31 to 1.81 per 100 000 person-years) disease. There was, however, some suggestion that the rate of increase may be slowing, especially for localized disease. A similar

Table 1. Esophageal cancer incidence among whites in nine SEER registries, 1975–1979 to 2000–2004*

Characteristic	1975–1979		2000–2004		% change in rate†
	No. of patients	Rate† (95% CI)	No. of patients	Rate† (95% CI)	
White males					
Total esophagus	1928	5.76 (5.49 to 6.03)	3943	8.34 (8.08 to 8.60)	44.8
Squamous cell	1303	3.81 (3.59 to 4.03)	889	1.90 (1.77 to 2.03)	−50.1
Adenocarcinoma	344	1.01 (0.90 to 1.13)	2706	5.69 (5.47 to 5.91)	463.4
Other and NOS	281	0.94 (0.83 to 1.06)	348	0.76 (0.68 to 0.84)	−19.1
Adenocarcinoma by stage					
Localized	65	0.20 (0.15 to 0.25)	692	1.48 (1.37 to 1.60)	640.0
Regional	101	0.28 (0.22 to 0.34)	892	1.86 (1.74 to 1.99)	564.3
Distant	111	0.31 (0.25 to 0.38)	884	1.81 (1.69 to 1.94)	483.9
Unstaged	67	0.22 (0.17 to 0.29)	238	0.53 (0.47 to 0.60)	140.9
Adenocarcinoma by age, y					
25–44	16	0.17 (0.10 to 0.28)	78	0.50 (0.39 to 0.62)	194.1
45–54	67	1.40 (1.08 to 1.78)	386	5.05 (4.55 to 5.57)	260.7
55–64	115	2.85 (2.35 to 3.42)	684	14.11 (13.07 to 15.21)	395.1
65–74	88	3.83 (3.07 to 4.73)	774	26.27 (24.45 to 28.19)	585.9
≥75	58	4.43 (3.36 to 5.75)	784	31.33 (29.17 to 33.60)	607.2
White females					
Total esophagus	855	1.93 (1.80 to 2.07)	1227	2.00 (1.89 to 2.12)	3.6
Squamous cell	622	1.38 (1.28 to 1.50)	589	0.98 (0.90 to 1.06)	−29.0
Adenocarcinoma	73	0.17 (0.13 to 0.21)	454	0.74 (0.67 to 0.81)	335.3
Other and NOS	160	0.38 (0.32 to 0.44)	184	0.29 (0.25 to 0.33)	−23.7
Adenocarcinoma by stage					
Localized	18	0.04 (0.02 to 0.07)	135	0.21 (0.18 to 0.25)	425.0
Regional	13	0.03 (0.02 to 0.05)	131	0.22 (0.18 to 0.26)	633.3
Distant	25	0.06 (0.04 to 0.09)	129	0.22 (0.18 to 0.26)	266.7
Unstaged	17	0.04 (0.02 to 0.06)	59	0.09 (0.07 to 0.11)	125.0
Adenocarcinoma by age, y					
25–44	2	—	15	0.10 (0.06 to 0.16)	—
45–54	7	—	36	0.47 (0.33 to 0.65)	—
55–64	12	0.28 (0.14 to 0.48)	79	1.57 (1.24 to 1.95)	460.7
65–74	26	0.83 (0.54 to 1.22)	100	2.89 (2.35 to 3.51)	248.2
≥75	26	1.07 (0.70 to 1.57)	223	5.20 (4.53 to 5.94)	386.0

* SEER = Surveillance, Epidemiology, and End Results; CI = confidence interval (generated by the Tiwari method) are 95% for rates; NOS = not otherwise specified; — = statistic could not be calculated because the rate was based on fewer than 10 cases.

† Rates are per 100 000 person-years, age-adjusted to the 2000 US standard population.

pattern was observed for women, although the rates were much lower for each stage (ranging from 0.06 or less per 100 000 person-years in 1975–1979 to 0.21–0.22 per 100 000 person-years in 2000–2004).

Over the three decades studied, the increases in adenocarcinoma occurred across all age groups. Among men, the greatest rates of increase (about 600%) and the highest rates were observed for the two oldest age groups, those aged 65 years or older. Rates also increased across all age groups among women, and the slopes appear remarkably parallel.

This study has several limitations. Cases of adenocarcinoma of the esophagus may

have been missed or misclassified, but this is unlikely because quality control efforts regarding case finding, abstracting, and coding have been an integral part of the SEER program since its inception (1). Data for the most recent years may be underreported, and SEER has estimated delay-adjusted rates in many instances. Thus, the upward trends in adenocarcinoma may be even more pronounced than what we have reported. The pathological diagnoses were not reviewed centrally, but the microscopic distinction between adenocarcinoma and squamous cell carcinoma has been recognized for decades. Furthermore, declines in the histological type category

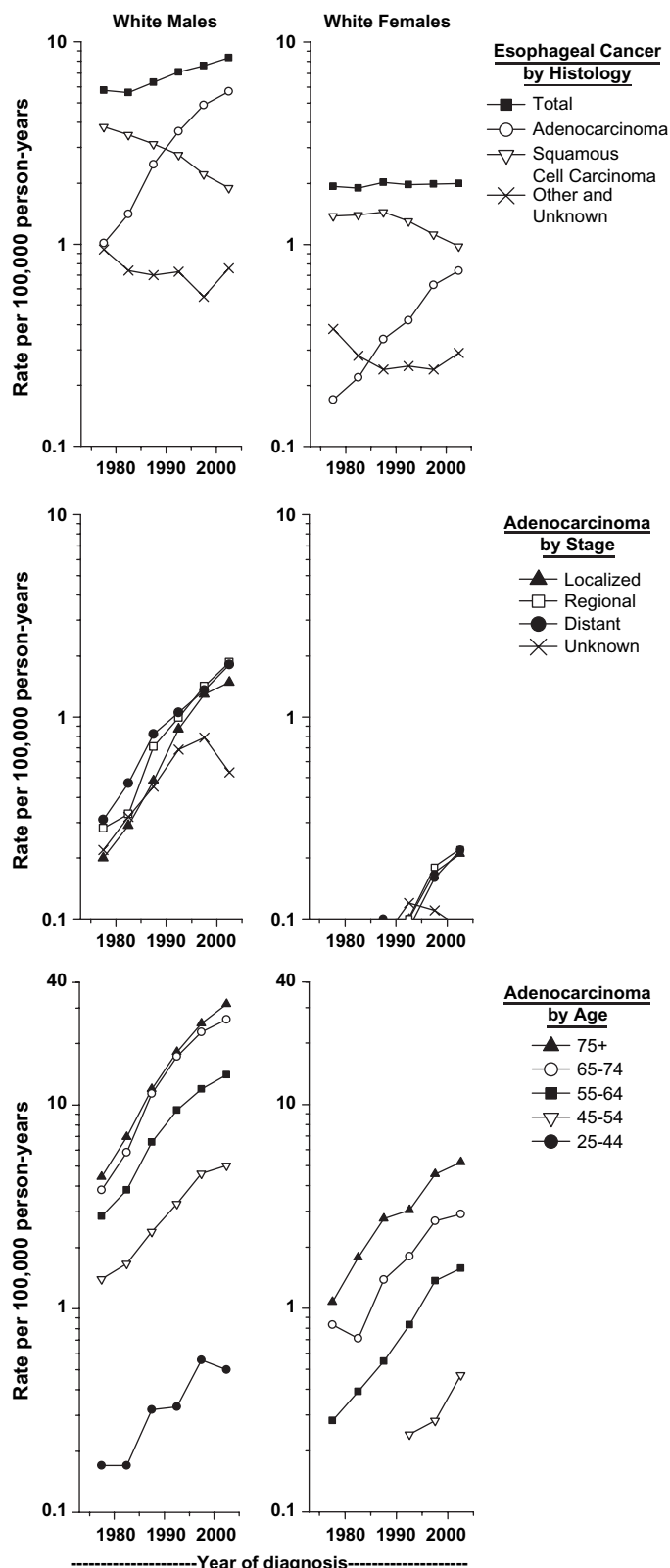


Figure 1. Trends in age-adjusted (2000 US standard) esophageal cancer rates across six 5-year periods, from 1975–1979 through 2000–2004, among white individuals by sex. Data are from nine Surveillance, Epidemiology, and End Results Registries. For adenocarcinoma rates by age group, ages are shown in years. For 95% confidence intervals for the earliest and latest points plotted, see Table 1.

other and not otherwise specified that might indicate improving specificity of the diag-

noses were modest and could not explain the observed increases in adenocarcinoma.

Adenocarcinoma rates are rising rapidly and at a similar pace among both white men and women. This increase was not clear in earlier reports (3–6) because of the rarity of adenocarcinoma among women. Improving diagnosis or increasing exposures may be affecting both sexes. All rates by stage rose at similar paces; however, the rate of increase may be slowing, especially for localized disease, indicating that the overall increase in adenocarcinoma incidence is unlikely to reflect heightened surveillance and earlier diagnosis. The increases appeared across all age groups, and the slopes were remarkably similar to each other. The parallel upward trends by age groups make it difficult to determine whether the patterns are reflecting only period effects, as observed for prostate cancer and prostate-specific antigen screening (10), or whether birth cohort effects may play a role, as observed convincingly for lung cancer and cigarette smoking (11,12). An earlier analysis that developed multistage carcinogenesis models by use of 1973–2000 SEER data indicated that the adenocarcinoma temporal trends were driven more by period than birth cohort effects (13).

Our findings are consistent with a Dutch study (14) that reported a substantial increase in Barrett esophagus, the precursor lesion for adenocarcinoma, that was not explained by changes in endoscopic practice or histopathological criteria. Although the exact mechanism is unclear, Barrett esophagus may be related to the higher intraabdominal pressure and increased prevalence of gastroesophageal reflux disease in obese individuals. We previously presented (6) data showing rapid increases in reflux disease among US veterans, with rates of increase that were similar to those for adenocarcinoma. Also, increases in obesity by age and sex since the mid-1970s appear to parallel increases in adenocarcinoma (15), and recent data (16) indicate that increases in obesity, particularly abdominal obesity, may account for part of the upward trend in the incidence of adenocarcinoma (13,17). Another reason for the increasing frequency of Barrett esophagus-associated adenocarcinoma may be the decreasing frequency of infection with *Helicobacter pylori*, which is associated with gastric atrophy and reduction in gastric acid secretion (18,19). Our data indicate that the increase in adenocarcinoma is real

and a growing health problem for both white men and women.

References

1. Ries LAG, Melbert D, Krapcho M, et al., eds. *SEER Cancer Statistics Review, 1975–2004*. Bethesda, MD: National Cancer Institute; http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER Web site, Accessed December 27, 2007.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics. *CA Cancer J Clin*. 2008;58(2):71–96.
3. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA*. 1991; 256(10):1287–1289.
4. Blot WJ, Devesa SS, Fraumeni JF Jr. Continuing climb in rates of esophageal adenocarcinoma: an update. *JAMA*. 1993;270(11):1320.
5. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer*. 1998;83(10):2049–2053.
6. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am*. 2002;11(2): 235–256.
7. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 9 Regs Limited-Use, Nov 2006 Sub (1973–2004)—Linked To County Attributes—Total U.S., 1969–2004 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.
8. SEER*Stat: Surveillance Research Program, National Cancer Institute SEER*Stat software, version 6.3.6 www.seer.cancer.gov/seerstat. Accessed December 27 2007.
9. Devesa SS, Donaldson J, Fears T. Graphical presentation of trends in rates. *Am J Epidemiol*. 1995;141(4):300–304.
10. Hsing AW, Devesa SS. Trends and patterns of prostate cancer: what do they suggest? *Epidemiol Rev*. 2001;23(1):3–13.
11. Devesa SS, Blot WJ, Fraumeni JF Jr. Declining lung cancer rates among young men and women in the United States: a cohort analysis. *J Natl Cancer Inst*. 1989;81(20):1568–1571.
12. Jemal A, Travis WD, Tarone RE, Travis L, Devesa SS. Lung cancer rates convergence in young men and women in the United States: analysis by birth cohort and histologic type. *Int J Cancer*. 2003;105(1):101–107.
13. Jeon J, Luebeck EG, Moolgavkar SH. Age effects and temporal trends in adenocarcinoma of the esophagus and gastric cardia (United States). *Cancer Causes Control*. 2006;17(7):971–981.
14. Post PN, Siersema PD, Van Dekken H. Rising incidence of clinically evident Barrett's oesophagus in The Netherlands: a nationwide registry of pathology reports. *Scand J Gastroenterol*. 2007;42(1):17–22.
15. National Center for Health Statistics. *Health, United States, 2007, With Chartbook on Trends in the Health of Americans*. Hyattsville, MD: National Center for Health Statistics; 2007.
16. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev*. 2008;17(2):352–358.
17. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(5): 872–878.
18. de Martel C, Llosa AE, Farr SM, et al. Helicobacter pylori infection and the risk of development of esophageal adenocarcinoma. *J Infect Dis*. 2005;191(5):761–767.
19. Corley DA, Kubo A, Levin TR, et al. Helicobacter pylori infection and the risk of Barrett's oesophagus: a community-based study. *Gut*. 2008;57(6):727–733.

Funding

Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics to LMB, SSD, and W-HC.

Notes

All authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

The authors thank Mr. John Lahey, Information Management Services, Inc, Rockville, MD, and Mr. David Check, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, for data tabulation and preparation of figures.

Manuscript received February 21, 2008; revised May 22, 2008; accepted May 23, 2008.